PATENT Attorney Docket No. BA-32448(1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	BAKER et al.
Serial No.	:	10/817,058
Filing Date	:	April 2, 2004
For	:	Method of Treating Cardiac Ischemia by Using Erythropoietin
Group Art Unit:		1653
Examiner	:	MAYER, Suzanne Marie
Confirmation No.:		2664

DECLARATION UNDER 37 CFR §1.131

Sir:

I, John E. Baker, Ph.D., being an inventor and applicant in the above-identified patent application, declare and say as follows:

1. That on a date prior to December 29, 2000, I, Dr. John E. Baker, conceived of a method of increasing resistance of the heart to injury from ischemia utilizing erythropoietin. This is evidenced, at least in part, by attached **Exhibit A**, which is a copy of a page of a research notebook dated *May 29, 1998*, with my observations and notes of a presentation on the identity of known triggers of the late phase of ischemic preconditioning. The notebook page includes my notation of the use of erythropoietin (EPO) to confer late preconditioning against injury from ischemia.

2. That from the date of conception prior to December 29, 2000, I, Dr. John E. Baker, in part with Dr. Yang Shi, diligently pursued this invention up to the date of filing the provisional application S/N 60/460,684 to the above-identified patent application in the U.S. Patent and Trademark Office on April 4, 2003, as evidenced by the following documents, attached as **Exhibits B-F**.

   a) Research articles published between *2000-2003*, presenting the results of an NIH-funded study (HL54075, funded 1997) to identify the signaling mechanisms stimulated by chronic hypoxia that result in protection of the heart against injury from ischemia, which resulted in the identification of the signaling mechanisms

stimulated by chronic hypoxia resulting in protection of the heart against injury from ischemia. The NIH-funded study provided a basis for testing the ability of erythropoietin to cause increased protection of the heart against injury from ischemia.

(i) Eells et al., "Increased Mitochondrial K_{ATP} Channel Activity During Chronic Myocardial Hypoxia" *Circulation Research* 87: 915-921 (*2000*), reporting NIH-funded study data showing mitochondrial K_{ATP} channels mediate cardioprotection in chronically hypoxic hearts (**Exhibit B**).

(ii) Kong et al., "Sarcolemmal and Mitochondrial K_{ATP} Channels Mediate Cardioprotection in Chronically Hypoxic Hearts," *Journal of Molecular and Cellular Cardiology* 33: 1041-1045 (*2001*), reporting NIH-funded study data showing that both sarcolemmal and mitochondrial K_{ATP} channels contribute to cardioprotection in chronically hypoxic hearts (**Exhibit C**).

(iii) Shi et al., "Chronic Hypoxia Increases Endothelial Nitric Oxide Synthase Generation of Nitric Oxide by Increasing Heat Shock Protein 90 Association and Serine Phosphorylation," *Circulation Research* 91: 300-306 (*2002*), reporting NIH-funded study data relating to a role for nitric oxide in protecting chronically hypoxic hearts against injury from ischemia (**Exhibit D**).

(iv) Rafiee et al., "Activation of Protein Kinases in Chronically Hypoxic Infant Human and Rabbit Hearts: Role in Cardioprotection," *Circulation* 106: 239-245 (*2002*), reporting NIH-funded study data on infant human and rabbit hearts adapted to chronic hypoxia through activation of protein kinases and pathways that may be responsible for protecting the chronically hypoxic heart against injury from ischemia-reperfusion (**Exhibit E**).

(v) Rafiee et al., "Cellular Redistribution of Inducible Hsp70 Protein in the Human and Rabbit Heart in Response to the Stress of Chronic Hypoxia: Role of Protein Kinases," *Journal of Biological Chemistry* 278: 43636-43644 (*2003*), reporting NIH-funded study data showing the expression and distribution of heat shock

proteins in chronically hypoxic hearts are influenced by several protein kinases (**Exhibit F**).

b) A research study conducted under the direction and supervision of Dr. Yang Shi and me, Dr. John E. Baker, on or about *December 19, 2001*, of formulations of erythropoietin (EPO). This is evidenced at paragraphs 4 and 5d of attached **Exhibit G**, which is a copy of the Discovery Record and Report entitled "Cardioprotection by Erythropoietin" that we wrote, had witnessed, and submitted to the Medical College of Wisconsin (MCW) Research Foundation on *May 9, 2002*. As set forth in the "Brief description of the discovery" attached to **Exhibit G**, in the study(ies), hearts isolated from rabbits were perfused with a range of concentrations of EPO prior to a global ischemic insult followed by reperfusion. The results of the study(ies) showed cardioprotection by the administration of EPO.

c) A *2001* Research Proposal entitled "Erythropoietin, Nitric Oxide Synthase and Resistance to Myocardial Ischemia," by John E. Baker, Ph.D., dated *2001*, which was initialed by Dr. Baker, copy of which is attached as **Exhibit H**.

4. That on *April 4, 2003*, the provisional application S/N 60/460,684 to the above-identified patent application, entitled "Method of Treating Cardiac Ischemia by Using Erythropoietin," was filed in the U.S. Patent and Trademark Office.

5. I further hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date: June 16, 2006 By: John E. Baker

John E. Baker, Ph.D.